INTESTINAL STEM CELL CONSORTIUM (ISCC)
Ancillary Studies Guidelines
PA-16-062

Prior to full submission of an Ancillary Study application for funding consideration, the ISCC Steering Committee (SC) will evaluate preliminary proposals (3 pages) that enhance the ability of the ISCC: [1] to identify, compare and characterize intestinal stem cells; and [2] to address other important questions related to intestinal stem cells and intestinal health and disease.

Definition of Studies Ancillary to the ISCC

There is a program announcement PA-16-062 (reissue of PAR-13-066 and PAR-11-107) titled "Ancillary Studies to the NIDDK Intestinal Stem Cell Consortium (R01)" which solicits grant applications from qualified investigators to conduct ancillary studies with the ISCC (http://grants.nih.gov/grants/guide/pa-files/PA-16-062.html).

Ancillary studies propose questions and test hypotheses that are relevant to the goals and purposes of the ISCC but are not addressed by the ISCC-funded Coordinating Center (CC) and research studies. An ancillary study, by definition, derives its financial support from sources other than the funds awarded by NIDDK for support of the ISCC. While ancillary studies will generally utilize information, data, materials, techniques or other resources of the ISCC, they may involve additional study sites, investigators, materials or data. The ISCC Ancillary Studies mechanism is not intended as a mechanism to support pilot studies.

The ISCC will devise new methods, collect novel data, and develop techniques to study potential populations of intestinal stem cells. To make the best possible use of this extraordinary resource, the ISCC encourages non-ISCC investigators to develop ancillary studies in conjunction with the consortium and to involve other investigators, within and outside of the ISCC, in this process. Each ancillary study must include at least one ISCC Principal Investigator or Co-investigator in a collaborative role and must have the approval of the contact Principal Investigator at each ISCC site proposed to participate in the ancillary study protocol. Studies that include substantial collaboration outside of the ISCC are encouraged.

The ISCC SC will conduct an initial review of all proposed ancillary studies. Ultimately, the SC must evaluate and approve or disapprove all ancillary studies. The SC will ensure that the ancillary studies do not impose an unacceptable burden on the ISCC staff or overlap or conflict with the aims of the ISCC. Data collection for funded ancillary studies may not proceed without the approval of the SC.

Submission of an Ancillary Studies Proposal

All ancillary studies proposals must be submitted to the SC through the ISCC CC to:

Jessica Girard, M.P.H.
Project Manager
Intestinal Stem Cell Consortium - Coordinating Center
City of Hope
Department of Information Sciences
1500 East Duarte Road
Duarte, CA 91016
Phone: 626-218-1600
E-mail: jgirard@coh.org

Timing of Submissions: Preliminary proposals (3 pages) should be submitted to the SC no less than 6 weeks prior to the NIH submission date to assure that ISCC approval can be secured in time to dovetail with the NIH process. The ISCC will make every effort to complete review of such proposals by its Steering Committee, allowing successful applicants time to prepare and submit applications for funding. Note that detailed scientific reviews of such proposed ancillary studies will be conducted by the NIH Study Sections.

Applicants should follow instructions in the program announcement (PA-16-062) document as well as in these guidelines to apply for ancillary studies to the ISCC. Deadlines for the various steps in the evaluation process for Ancillary Studies that are intended for submission to NIH under any of the standard deadlines are indicated in **Table 1**. During the application preparation phase, applicants are encouraged to contact the CC for data management and analytical support, as needed.

Ancillary studies that will seek funding from a source other than NIH should be submitted to the ISCC for its approval at least six months prior to the intended project starting date, allowing the ISCC to conduct its own evaluation. See the additional guidelines for submission of ancillary studies that will not go through NIH peer review (**Appendix A**).

Table 1: ISCC Ancillary Study Applications: Timeline Related to NIH Submission Deadlines

Ancillary Applicant Action Item	Time Prior to NIH Submission Deadline
3-page preliminary proposal to CC for SC review	6 Weeks
NIH R01 submission deadline	As published

The Preliminary Proposal

Proposals for all ancillary studies must be submitted to the CC for review by the SC. A cover letter of no more than one page should indicate why the proposed study should be conducted as an ancillary study to the ISCC rather than as a separate and independent project.

Proposals should be concise, but contain sufficient detail to allow a thorough assessment of the relevance of the proposal to the goals of the ISCC, its scientific importance and possible impact, as well as any added workload for the ISCC investigators. We expect that typical proposals will be approximately 3 pages in length, single spaced in an easily readable type font on 8½ x 11 inch paper with one inch margins on all sides. The components of the proposal should include:

[1] Project Title

[2] List of Principal and Co-Investigators by name and institution

[3] Clear statement of the hypotheses to be tested

[4] An abstract section including: (a) Background, (b) Specific Aims, (c) Outline of the protocol, (d) List and brief description of any non-routine analytical methods employed, and (e) Informative reference citations.

[5] List of any collaborating ISCC or non-ISCC sites. Close collaboration with the participating ISCC sites through the entire process is highly encouraged. Discussions with ISCC PIs must take place within the context of their confidentiality agreements and, thus, must include all ISCC investigators whose work, materials or data are involved. The proposal must be accompanied by letters from the PIs of all collaborating ISCC projects and any other collaborating scientists indicating their roles in the project and their willingness to participate. Once NIH submission and peer review is completed, and funding decisions are made, participating ISCC sites must once again confirm their participation in the proposal and if participation is not possible at that time, another willing ISCC site may be substituted with the consent of the ISCC Steering Committee.

[6] Indication of numbers and sizes or amounts of biological samples required, techniques, data or other resources to be accessed, including involvement required from the ISCC CC.

[7] ISCC parent study and burden: Describe the impact of the study on ISCC studies. Provide details on the time and effort required of ISCC research sites and CC.

[8] Projected costs/budget: The proposed budget and intended funding source for project. Provide evidence that the proposed budget will be sufficient to complete the project. Include costs for CC participation as needed. During the course of an ancillary study, the ISCC SC may determine that it would be beneficial to the ISCC or the ancillary study to have the ancillary study PI participate in some SC meetings. The budget for the ancillary study may include a request to support travel for such participation in up to one meeting per year during the course of the study. The ancillary study PI should commit in both the preliminary application and the final application to attend these meetings as requested.

[9] Future participation: if the ancillary study would be in progress beyond the lifetime of the ISCC, ensure that the budget covers any necessary costs and that the commitment from the collaborating ISCC PIs includes commitment beyond the life of the ISCC study if necessary.

[10] Sharing: the application must contain a statement that data and resource sharing from the ancillary study will be under the same terms as for the ISCC, as described in the original ISCC RFA-DK-08-010 and the ISCC renewal RFA-DK-13-012 (http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-13-012.html).

Ancillary Study Review Process

SC Review Criteria: In determining initial approval, the SC will give priority to studies which: (1) contribute to the ISCC aim of examining a broad range of relevant research questions relevant to intestinal stem cells in health and disease; (2) make important use of the unique ISCC resources, data and collaborative opportunities; (3) do not interfere with or duplicate the main ISCC studies or those of other accepted ancillary studies; (4) produce minimal burden on ISCC investigators and minimal demand on ISCC resources that are also required for accomplishing the goals of the major ISCC protocols; (5) have valid scientific merit; and (6) could not readily be accomplished as separate projects independent of the ISCC. It is a goal of the ISCC to facilitate as many high-quality ancillary proposals as possible. In general, the Ancillary Study mechanism is not suited to pursue pilot studies which may be conducted at single sites without the need for consortium resources. Close collaboration with the participating ISCC sites is necessary throughout this process.

Initial Evaluation: The SC will review submitted proposals at least monthly. The ISCC will not carry out an in-depth scientific review of proposals. This will be accomplished by the normal peer review process (e.g. NIH study section). Rather, the SC will focus on the feasibility, overlap with ISCC projects, and burden on ISCC research projects and the CC. Proposals will be categorized by the SC into six groups, in order of decreasing interest to the ISCC:

1) The ancillary study's aims are fully consistent with the overall goals of the ISCC, while distinct from those being addressed by the major ISCC aims or studies. The proposed study makes unique and valuable use of ISCC assets, may involve collecting novel samples, and may also use data or samples collected for the main ISCC studies. Such studies may be approved.

2) The ancillary study's aims supplement those addressed by the major ISCC aims or studies. They may utilize data from the core database, may involve collection of at least some novel data not collected for the major ISCC studies, and may utilize ISCC resources and data. Such studies may be approved.

3) The ancillary study's aims are already addressed to some degree within the ISCC main, pilot, or ancillary study aims. Such studies are unlikely to be approved unless the overlap with other studies is minimal.

4) The ancillary study's aims are outside the interests of the ISCC. Such studies will not be approved.

5) The ancillary study's aims could be met by an independent project, and do not require an affiliation with the ISCC. Such studies will not be approved.

6) Irrespective of the relevance of the study's aims, an ancillary study that will make unacceptable demands on ISCC investigators or resources will not be approved.

Scientific Review: Proposals in categories 1 and 2, and possibly some in category 3, will be further evaluated by the SC prior to their initial approval. The SC review of proposals that will be submitted to the NIH will include a preliminary review of scientific merit, but will focus on the feasibility of the study for the ISCC and an assessment of overlap or interference of work already being completed in the ISCC. This review is not meant to provide extensive scientific feedback to applicants. The latter will be obtained as a result of the detailed scientific review occurring through the NIH peer review system.

For other proposals including industry-sponsored ancillary studies, if no other acceptable peer review has taken, or will take place, the SC, supplemented with other experts as necessary, will conduct an in-depth scientific review of a proposal. This review process is outlined in Appendix A of the guidelines.

During SC review, ancillary studies proposals will be circulated to the Contact PIs of the ISCC for comment. Interested ISCC investigators may contact the PI of the proposed ancillary study and request participation as collaborators in the study. In addition, as appropriate, the SC may recommend that the ancillary PI consider adding additional sites depending on scientific requirements and benefits.

Initial approval will be based, in part, on whether the ancillary study interferes with the ISCC studies and whether it competes with other proposed ancillary studies. To maximize efficient use of expertise and other resources, the SC may recommend that several similar and potentially competing ancillary study proposals be combined. The SC will determine which ancillary study will receive initial approval if several meritorious proposals compete for the same ISCC resources.

Conditional Approval: If the SC determines that a proposal contains elements that, if adjusted, would allow for approval, it will be given conditional approval and the PI will be notified with a list of changes to be made to gain SC initial approval.

Protocol Changes: Applicant PIs must notify the SC through the ISCC project coordinator no less than 4 weeks before the submission deadline of the proposals of any substantial changes from the approved 3 page application that appear in the final proposal. This applies whether the changes are investigator initiated or are made due to recommendations from a review group such as the SC. Substantial changes include, but are not limited to, change of sites, PIs, endpoints, hypotheses, data items, major changes in sample sizes, and merging of applications. These modifications must be conveyed to the ISCC coordinator electronically highlighting modified sections.

In all instances of substantially altered applications, the SC will re-evaluate and determine whether the modified project still merits SC support as an ISCC-approved Ancillary Study. The ISCC will compare all final applications with approved, preliminary 3-page applications. SC approval for submission will be withdrawn from any applications that contain appreciable but previously undisclosed modifications at that time.

After a study is approved, significant protocol changes must be reported to the SC and approved by the ISCC SC. Failure to do so, may lead to the withdrawal of ISCC support.

Studies Proposing to Use ISCC Resources: Initial SC approval for an ancillary study to use ISCC resources will be contingent upon the availability of the requested resources beyond the needs of core ISCC protocols and approved ancillary studies already underway. An additional consideration for such studies is the importance and uniqueness of the study, should its approval and subsequent use of the resources deplete them.

Failure to Obtain Funding: If, within 10 months of initial approval by the Steering Committee, an investigator is unsuccessful in obtaining the necessary resources to conduct a study, the initial Steering Committee approval of the project will generally be withdrawn and the Steering Committee will consider other proposals to use these resources and expertise. Investigators are required to inform the CC of funding decisions within 5 working days of their receipt. If unsuccessful, and the investigator plans on submitting a revised application, the following steps should be taken:

1) Within 60 days of summary statement receipt, the ancillary study applicant sends a simple letter to the ISCC stating an intent to re-submit and the expected timeframe for re-submission
2) At least 30 days before re-submission to the NIH, the ancillary study applicant sends a letter to the ISCC stating a) if any important changes have been made to the previously approved project/aims, and b) any changes required by or offered to the ISCC.
3) Within one week of receiving 2) above, ISCC SC sends a letter to the investigator confirming the status of the revised proposal.

If the SC approves the revised application, the SC may keep the required resources available for the project for a further 8 months, allowing time for submitting a revised application. However, the SC reserves the right to reallocate these ISCC resources for another approved project. In the absence of a revised application, the initial approval for the project will be withdrawn.

Conflict of Interest: If any SC member proposes an ancillary study, collaborates with an investigator who proposes an ancillary study, or is affiliated with the institution of an investigator who proposes an ancillary study, he or she will be recused from considering that proposal, similar to NIH peer review policies for avoidance of actual or perceived conflicts of interest.

Duration of Initial SC Approval: Initial ISCC approval of any application is considered for only one application for funding, with a date to be stipulated in the application and resulting ISCC approval statement. Investigators submitting a revised application must renew their ISCC approval by submitting a new 3-page proposal to the ISCC in accordance with the schedule indicated in **Table 1**, if any important changes have been made to the previously approved project/aims. If no such modifications are being proposed, then the procedures outlined above under “Failure to Obtain Funding” shall be followed.

Final Steering Committee Approval

Following peer review, the Steering Committee will consider several additional issues before granting final approval to conduct an ancillary study.

IRB Approval: All ancillary studies must receive necessary approvals from IRBs or IACUCs at the institutions involved. Documentation of IRB and/or IACUC approval must be submitted to the ISCC CC before an ancillary study can be initiated in conjunction with the ISCC.

Confidentiality: If studies include human subjects, confidentiality of individually identifiable data about ISCC participants must be assured.

Availability of Funding: For ancillary study applications to NIH or other organizations for funding, initial approval by the SC constitutes approval to apply for such funding. Final approval requires submission by the ancillary study PI to the CC of documents establishing a definite commitment for funding. However, because several applications that compete for ISCC resources may receive funding, receipt of such funding does not

guarantee final SC approval. In these circumstances the SC would work with the relevant PIs to find compromises that would allow the funded applications to proceed in a way that would not place an unacceptable burden on ISCC investigators or other resources prior to awarding of final SC approval.

No data collection or use of ISCC data or other resources may begin without final approval from the SC.

Ancillary Studies Must Provide Funding for Hidden Costs: In assessing the acceptability of an ancillary study proposal, the SC will be concerned with both the explicit and the hidden costs to the ISCC entailed by the proposal (e.g., burden or other costs to the CC for additional data collection and statistical support, burden or other costs to research projects for sample or data collection and shipping). The ancillary study's PI should provide evidence that adequate support for carrying out all functions required for the ancillary study will be available and that the ancillary study will not add any additional, unfunded cost to the ISCC.

Post Funding Confirmation of ISCC Sites' Participation: Prior to final SC approval of a funded proposal, each ISCC site that is participating must reaffirm their interest and ability to participate in the study. If an ISCC site cannot participate, another willing site may be substituted with the consent of the ISCC SC.

Approval Notice: Once final SC approval is received, the SC Chair will distribute a signed approval notice to the submitting PI. If the Chair is conflicted, or unavailable, the Coordinating Center PI will provide signature of the approval notice.

Data Issues

The release of any ISCC data from the CC or an ISCC parent project to an ancillary study investigator is subject to the rules regarding release and use of data defined in the ISCC confidentiality policy and sharing agreements.

In general, all data collected by the ancillary study, or a link to such data, must be provided to the ISCC CC electronically and in timely fashion for integrating into the ISCC database and/or web site, ultimately, archived with the other ISCC data. The ancillary study PI will be given the first opportunity to analyze, present, and publish data collected for the specific aims of the ancillary study. After a reasonable time (in general, 18 months after the ancillary study initiation or initiation of the particular experiment), the ancillary study data will be made available for additional uses by ISCC investigators, in collaboration with the ancillary study investigators. It is the responsibility of the ancillary study PI to state to the Steering Committee in writing in advance of beginning the study any special circumstances that would make these guidelines for data sharing impossible or undesirable. Reasonable and justified requests for limiting Steering Committee access to the data will be considered. In addition, the acquisition or analysis of specialized data sets, such as high-throughput genotyping or microarray data, involving the CC may be negotiated between the PI of the ancillary study and the CC prior to granting by the Steering Committee of final permission to proceed with the study.

Additional samples and resources from the ancillary study will be made freely available to the ISCC by the ancillary study investigators.

Additional Data and Resource Requests for Funded Ancillaries: Funded ancillary studies seeking to receive data from the main ISCC study which were not requested in the original proposal must submit a written request through the SC. The request must include a precise description of the data requested, a justification for the receipt of such data, an explanation of the use and preliminary plans for analyzing and reporting the additional data. The ancillary study PI is responsible for working with the CC and the collaborating ISCC study to determine any impact that the additional data might have on CC and ISCC operations, and for covering the costs incurred.

The SC will review the proposal to determine final approval.

Renewal Requests for Funded Ancillaries: Funded ancillary studies seeking to obtain a renewal for their grant should notify the CC. If the specific aims of the study change or the protocol is fundamentally altered, the new proposal will have to go through the review process for new studies. Changes will need to be detailed in brief summary format along with scientific justification (3 pages or less) and submitted to the CC along with a copy of the original study protocol. The CC will review the changes to determine if additional resources will be required. The proposed study will also undergo SS review with recommendation to the SC.

Non-NIH sponsored Ancillary Studies

Proposals for ancillary studies that will seek funding from sources other than NIH will be evaluated in accordance with the procedures described above. It is the responsibility of the PI to obtain agreement from the sponsor through an appropriate contractual mechanism that all data will be provided to the ISCC to combine with ISCC data. Study conduct must comply with all existing ISCC, individual institutions within the ISCC, and NIH policies and guidelines. Specifically, the sponsor may not interfere with analysis or publication of any data obtained during the course of an ancillary study to the ISCC. The ancillary study PI should contact the NIDDK project scientist before beginning substantive discussions with any potential industry sponsor. Involvement of a study with industry may require a Cooperative Research and Development Agreement (CRADA).

Publications and Presentations

Proposals for all abstracts, presentations, and publications from an ancillary study must be submitted for review and approval by the ISCC Publications Authorship Subcommittee prior to submission or presentation, in accordance with the ISCC rules for publications and presentations.

Each manuscript and abstract is generally expected to include an ISCC investigator as co-author, except under circumstances that should be stated and justified as part of the original submission to the SC.

All publications, presentations, and abstracts derived from an approved ancillary study must acknowledge support from the ISCC grants as well as the specific support for the ancillary study.

Acknowledgement
In drafting these guidelines, the ISCC SS had the benefit of ancillary studies guidelines developed previously for other NIH-funded research consortia. Specifically, both concepts and, in some instances, specific language were borrowed from ancillary studies policies developed for the NIDDK and NHLBI-sponsored Virahep-C project, the LOOK Ahead and Halt C Trials, the LABS consortium, and the NASH CRN.

Appendix A: Guidelines for Ancillary Studies that will not Undergo NIH Peer Review

This policy describes the guidelines and procedures applicable to ISCC ancillary study proposals that will not be reviewed by an NIH Study Section. In such situations, the SC, supplemented with other experts as necessary, will conduct its own in-depth scientific review of the proposal. Application submission guidelines and review procedures are outlined below.

A. General Guidelines

Ancillary study proposals submitted for this in-depth scientific review should be easily read and understood by individuals who may not be experts in the scientific area of research, but who are sufficiently knowledgeable in scientific areas related to the research to be able to evaluate the proposal fairly. These ancillary study proposals should contain sufficient detail to allow adequate scientific review and assessment of the relevance of the proposal to the ISCC studies, as it impacts all aspects of the ISCC. The conceptual framework, design, methods, and analytical procedures should be adequately developed, well integrated, well reasoned, and appropriate for the aims of the project.

B. Application Format

Each application should include:

1. List of all investigators, their proposed role in the study, and their biographical sketches (limited to 2 pages each).

2. Description of the resources and environment for conducting the study (< 1 page).

Items 3-9 below should be no more than 15 pages in length using Times New Roman Font 10

3. Introduction

This section should provide background information with pertinent key references. It should also clearly outline the significance of the research question and how the outcome(s) of the study will advance scientific knowledge and/or clinical practice. The introduction must indicate why the ISCC consortium is necessary to perform the proposed work.

4. Hypotheses and specific aims

5. Research design

This section should describe the overall research design and implementation plan. It should also clearly delineate the activities/role(s) required of ISCC personnel, laboratories, Coordinating Center, and other relevant parties and facilities. A timeline (including anticipated start date, enrollment period [if applicable], sample collection period [if applicable], and analysis period at a minimum) should be provided.

6. Methods

This section should provide a concise description of the methods to be employed. The feasibility and limitations of the project should also be addressed.

7. Data analysis

At a minimum, this section should include a power analysis and a description of the analytical plan. It should also identify any limitations inherent within the analytical plan.

8. Risk and Safety concerns

A completed section on Human Subjects and/or Vertebrate Animals according to PHS form 424 instructions must be included. Discuss the importance of the knowledge to be gained as a result of the proposed research. Discuss why the risks to subjects are reasonable in relation to the importance of the knowledge that reasonably may be expected to result. Include an Informed Consent document (draft

only, IRB approval not required), if applicable, as well as a Data and Safety Monitoring Plan (for more information on how to create one, please see: http://www2.niddk.nih.gov/Research/ClinicalResearch/ClinicalResearchDataandSafetyMonitoringPolicy.htm.

9. Impact on the ISCC parent study
    a. List of proposed sites
    b. ISCC resources required to conduct the ancillary study
    c. Relevance to ISCC hypotheses and interpretation of results
    d. Impact on the CC for data management and analysis, web site and other coordination activities

C. Receipt Timeline

Ancillary study proposals must be submitted no less than 6 months prior to a funding source submission and/or starting date if funding has already been secured.

D. Application Review Process

Applications are to be submitted to the ISCC CC. Upon receipt, the CC will review the application to ensure that all the sections required above are included. Incomplete applications will be returned to the applicant for revision and resubmission, if appropriate. The 6-month receipt deadline is for a complete application.

Proposals deemed complete by the CC will be forwarded to the ISCC SC for a two-tiered review process. The SC will conduct an initial review of the research question to assess the relevance of the proposed study to the ISCC. Applications **may be rejected at this point without further scientific review.**

Following initial review, the SC may recommend a more in-depth review of the application. This in-depth review will be conducted by at least three reviewers with appropriate subject-matter expertise. Reviewers may be selected by the SC from within the ISCC or from non-ISCC researchers with relevant expertise. Conflict of Interest will be evaluated on each reviewer. Reviewer expertise may include, but is not limited to, the scientific area(s) of the proposed ancillary study, analytical/statistical procedures, study design and relevant methodological procedures.

The proposed study will be evaluated using the NIH criteria and scales. Each reviewer will be asked to provide a critique of the study and score from 1-9. The SC will use the reviewers' critiques and scores to recommend approval or disapproval.